UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,871	04/11/2005	Hans-Georg Kreysch	MERCK-2990	4478

23599 7590 06/01/2007

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

MAIL DATE	DELIVERY MODE
06/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,871	KREYSCH ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/05;* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-29 are pending.

2. Applicant's election with traverse of Group 1, Claims 1-28 drawn to a pharmaceutical composition comprising a first and a second antibody molecule, or a portion thereof, having the capability to bind to different epitopes located on the same ErbB receptor molecule types, wherein said first antibody molecule or a portion thereof, comprises binding sites that bind to a first specific epitope on the ErbB 1 receptor molecule type, and said second antibody molecule comprises binding sites that bind to a second specific epitope on the same ErbB 1 receptor molecule type, a kit comprising said first and second antibody molecules, filed 3/8/07, is acknowledged. The traversal is on the grounds that a search of all the claims would comprise overlapping subject and can be made without serious burden. Applicants further submit that the restriction requirement should be modified to combine Group II (claim 29), drawn to a method of using the claimed pharmaceutical composition. If the product claim is found allowable, process claims that depend from or otherwise require all the limitations of the patentable product may be rejoined." See M.P.E.P. § 806.05.

The request for rejoinder of Group 2, drawn to a method of using the claimed pharmaceutical composition upon allowance of product claims is acknowledged. However, no claims drawn to a product are allowable at this time.

The inventions listed as Groups 1-2 do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The WO 94/00136 publication (of record, January 1994; PTO 1449) teaches a composition comprising a combination of a first and second anti-erbB-2 such as monoclonal, chimeric, bispecific and/or single chain antibodies or binding fragment thereof that bind to different epitopes located on the same ErbB2 receptor (see claims 1-3 of the WO 94/00136 publication, page 6, DET.£ILED DESCRIPTION OF THE INVENTION, page 8, lines 1-24, in particular). The reference antibodies bind to the extracellular domain of the natural ligand binding domain (see page 12, lines 6-7, in particular) and inhibit tyrosine phosphorylation signaling (see page 10, second full paragraph, in particular). The WO 94/00136 publication teaches that a

combination of anti-receptor antibodies leads to different and more potent anti-tumor activities than single antibody (see page 10, last paragraph, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the pharmaceutical composition wherein the first and second antibodies bind to different epitopes located on the same ErbB 1 receptor instead of ErbB2 receptor.

The US Pat No 5,705,157 (of record, issued Jan 6, 1998; PTO 892) teaches various monoclonal antibodies specific for the extracellular domains of EGFR (ErbB 1) such as MAb 425 and antibody to ErbB2 such as 7.16.4 for treating tumor (see entire document, col. 4, lines 64-67 bridging col. 5, lines 1-7, Abstract, in particular). The ' 157 patent teaches a combination of antibodies work synergistically to suppress tumor growth (see col. 3, lines 10-15, in particular). The US Pat 4,943,533 (issued July 1990; PTO 8792) teaches various monoclonal antibodies such as MAb455 and MAb 225 that bind to the different epitope on the same epidermal growth factor receptor (ErbB 1) where one antibody competes with the ligand for binding to the receptor and the other antibody binds to the receptor but does not compete with the ligand (see entire document, col. 3, line 46-53, col. 8 through 10, in particular). The reference antibody 225 inhibits the growth of A-431 tumor cells in the absence of ligand (see col. 8, lines 15, in particular). Therefore, it would have been obvious to one of ordinary skill in the art with the expectation of success in substituting the anti-erbB-2 antibodies in the pharmaceutical composition for treating tumor as taught by the WO 94/00136 publication for the MAb 425 antibody that binds to ErbB1 as taught by the ' 157 patent and the MAb 225 antibody that binds to ErbB1 as taught by the '533 patent for use as a medicament for treating tumor. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the WO 94/00136 publication teaches a combination of anti-receptor antibodies can lead to different and more potent anti-tumor activities than single antibodies (see page 10, last paragraph, in particular). The '157 patent teaches that MAb 425 antibody that binds to ErbB1 is useful for treating tumor and a combination of antibodies work synergistically to suppress tumor growth (see entire document, col. 4, lines 64-67 bridging c01.5, lines 1-7, Abstract, see col. 3, lines 10-15, in particular). The '533 patent teaches that monoclonal antibody 225 that binds to EGRF1 (ErbB 1) inhibits the growth of A-431 tumor cells in the absence of ligand (see col. 8, lines 15, in particular).

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art they do not have single general inventive concept and lack unity of invention. Therefore, the requirement of Group 1 (claims 1-28) and Group 2 is still deemed proper and is therefore made FINAL.

3. Claim 29 is withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to a non-elected invention.

4. Claims 1-28, drawn to a pharmaceutical composition comprising a first and a second antibody molecule, or a portion thereof, having the capability to bind to different epitopes located on the same ErbB receptor molecule types, wherein said first antibody molecule or a portion thereof, comprises binding sites that bind to a first specific epitope on the ErbB 1 receptor molecule type, and said second antibody molecule comprises binding sites that bind to a second specific epitope on the same ErbB 1 receptor molecule type, a kit comprising said first and second antibody molecules, are being acted upon in this Office Action.

5. The disclosure is objected to because of the following informalities: (1) "TGFa" at page 3, line 21 and page 4, line 15-16 should have been "TGFα"; (2) the phrase "binds to the same different epitope" at page 16, line 18 is ambiguous and indefinite because antibody binds to the same or different epitope, (3) the word "colcny" is misspelled; it should have been "colony". (4) The word "inhibitong" at page 29, line 15 is misspelled; It should have been "inhibitor". (5) the sentence "the identical receptor molecule is meant" at page 18 line 6-7 is incomplete and (6) duplicate "of both" on page 41 at line 10 should be deleted.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-11, 13-23, and 25-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a pharmaceutical composition comprising a first and second antibody or a binding fragment thereof wherein the first antibody or a binding fragment thereof that binds different epitopes on the same ErbB1 receptor wherein the first

antibody is a murine, chimeric or humanized MAb 425 and wherein the second antibody is a murine, chimeric or humanized MAb 225 for treating breast cancer, **does not** reasonably provide enablement for how to make and/or use any pharmaceutical composition comprising all first and second antibody molecules or any portion thereof, having the capability to bind to different epitopes located on same or different ErbB receptor molecule types or an immunoconjugated thereof wherein the first antibody portion is fused by its C-terminus to any biologically effective peptide, any polypeptides or any proteins, optionally via a linker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a pharmaceutical composition comprising a combination of two antibodies or a binding fragment thereof that binds to different epitopes on the extracelullar domain of ErbB1 receptor to which the ligand binds. These anti-EGFR (ErbB1) antibodies are murine MAb 425, humanized antibody (h425) thereof, chimeric antibody (c425) thereof or a binding fragment thereof, such as a F(ab')2, and murine MAb 225, humanized antibody (h225) thereof, chimeric antibody (c225) thereof or a binding fragment thereof such as a F(ab')2. Most preferred is the combinatorial application of humanized MAb 425 and chimeric MAb 225 as a whole antibody or as F(ab')2 fragment for a pharmaceutical composition, see page 6, lines 20-25. The pharmaceutical composition mentioned above further comprising a cytotoxic drug, cytokine, or a chemotherapeutic agent.

The specification does not teach how to make and use all pharmaceutical composition comprising any combination of first and second antibodies or any portion thereof other than the antibodies mentioned above having the capability to bind to different epitopes located on the same ErbB1 receptor molecule types for treating all cancer as broadly as claimed. There is insufficient guidance as to binding specificity associated with the structure, i.e., six CDRs of

immunoglobulin heavy and light chains for all first and second antibodies that bind to the different epitope on the same receptor ErbB1 type. The specification provides no guidance or working example of the use of other antibodies to treat any cancer other than the specific antibodies mentioned above.

With respect to the erbB1 receptor, McInnes et al (Biopoly 43: 339-366, 1997; PTO 892) teach that binding of erbB-1 ligand to their receptor involves multiple region of the receptor and there is no single epitope for conferring native affinity to this family of ligand (see page 345, col. 2, first full paragraph, in particular). McInnes concludes that "it is clear that there is no consensus as to which residues and regions comprises the receptor binding site and thus form the elements of the multidomain model for association" (see page 345, col. 2, first full paragraph, in particular).

A pharmaceutical composition for treating cancer without *in vivo* working example is unpredictable. Dermer et al (Bio/Technology 12: 320, 1994; PTO 892) teach that "Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapt to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference teaches that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interaction.

Gura et al (Science 278: 1041-1042, Nov 1997; PTO) teach the shortcomings of potential anti-cancer agents including extrapolating from *in vitro* protocols, the problems of drug testing for cancer is that the model system are not predictive at all. Given the lack of guidance and *in vivo* working example, it is unpredictable which combination of first and second antibodies that bind to different epitopes on ErbB1 is effective as a pharmaceutical composition for treatment of mammalian tumors. It is not predictable to one of ordinary skill in the art how to make and use all first and second antibodies that bind to different epitopes on the same ErbB1 receptors type for treating all cancer.

Further, the specification does not teach the structure of any peptide, or any polypeptide or protein without the amino acid sequence for use as an immunoconjugate other than the cytokine.

Stryer et al teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages). Without the amino acid sequence, there is no structure, much less function.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

8. Claims 1-11, 13-23, and 25-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) all first and second antibodies or portion thereof having the capacity to bind to different epitopes located on the same ErbB1 receptor molecule types for the claimed pharmaceutical composition other than the murine MAb 425, or humanized (h425) or chimeric (c425) version or a fragment thereof, such as a F(ab')2, and murine MAb 225, humanized (h225), chimeric (c225) version or a fragment thereof, such as a F(ab')2 that bind to different epitopes located on the same ErbB1 receptor, and (2) any peptide, any protein or polypeptide other than cytokine fused to or conjugated to all first and second antibodies.

The specification discloses only a pharmaceutical composition comprising a combination of two antibodies or a binding fragment thereof that binds to different epitopes on the

extracellular domain of ErbB1 receptor to which the ligand binds. These anti-EGFR (ErbB1) antibodies are murine MAb 425, humanized antibody (h425) thereof, chimeric antibody (c425) thereof or a binding fragment thereof, such as a F(ab')2, and murine MAb 225, humanized antibody (h225) thereof, chimeric antibody (c225) thereof or a binding fragment thereof such as a F(ab')2. Most preferred is the combinatorial application of humanized MAb 425 and chimeric MAb 225 as a whole antibody or as F(ab')2 fragment for a pharmaceutical composition, see page 6, lines 20-25. The pharmaceutical composition mentioned above further comprising a cytotoxic drug, cytokine, or a chemotherapeutic agent.

With the exception of the combination of the specific first and second antibodies mentioned above, there is insufficient written description about the binding specificity associated with the structure (the six CDRs 1-3 of immunoglobulin heavy and light chains) of first and second antibodies for the claimed pharmaceutical composition or kit, in turn, useful for treating all types of cancer.

Further, other than the cytokines and cytotoxic agent, there is insufficient written description about the structure associated with function of all fusion partners such as all peptide, protein, polypeptide that is linked to the first and/or second antibody molecules.

The specification discloses only a specific pharmaceutical composition comprising a specific combination of MAb 425, or humanized (h425) or chimeric (c425) or a binding fragment thereof and a monoclonal MAb 225, humanized (h225), chimeric (c225) or binding fragment thereof, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of first and second antibodies to describe the genus for the claimed pharmaceutical composition or pharmaceutical kit. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Modjtahedi et al (Cell Biophys 22(1-3): 129-146, Jan-June 1993; PTO 892).

Modjtahedi et al teach a pharmaceutical composition comprising a combination of a first antibody molecule such as rat monoclonal antibody ICR62 that binds to epitope C on the human EGF receptor and a second antibody such as ICR64 that binds to epitope D on the external domain of human EGFR (see entire document, abstract, page 139, last paragraph, Figure 5, in particular). The reference antibodies inherently inhibit the binding of natural ligands such as EGF and TGF from binding to the EGFR and thereby inhibiting the growth of HN5 xenograft tumors in athymic nude mice (the reference EGFR is also known as ErbB1) (see abstract, in particular). The reference epitopes C and D to which the reference antibodies bind inherently located within the EbB1 receptor binding domain. Thus, the reference teachings anticipate the claimed invention.

11. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by US Pat No 5,705,157 (of record, issued Jan 6, 1998; PTO 892).

The '157 patent teaches a pharmaceutical composition comprising at least one antibodies specific for epidermal growth factor receptor (also known as ErbB1) and at least one antibody that binds to p185c-neu (also known as ErbB2 or HER2 or EGFR2) for treating tumor (see claim 4 of the '157 patent). The term "at least one" implies the reference composition comprising one or more antibodies of the same ErbB1 receptor type. The term "comprising" is open-ended. It expands the claimed pharmaceutical composition to include additional antibodies such as one or more antibodies that bind to p185c-neu as taught by the '157 patent. The '157 patent teaches an antibody that binds to the extracellular domain of human EGFR such as a monoclonal antibody MAb425 and it inhibits EGF binding to its receptor and induces EGF receptor down-regulation without stimulating EGF receptor tyrosine kinase activity (see claim 4 of the '157 patent, col. 12, line 7-11, in particular). The '157 patent teaches another monoclonal antibody that binds to EGFR such as M294 from ICN biomedicals (see col. 7, lines 38-40, in particular). The '157 patent teaches monoclonal antibodies that bind to the extracellular domains may be selected by screening for binding to the extracellular domains of EGFR (see col. 4, lines 64-67 bridging col. 5, lines 1-7, col. 2, lines 37-42, in particular). The reference EGFR extracellular domains to which the reference antibodies bind are located within the EGF ligand binding domains because the reference antibodies such as MAb425, chimeric antibodies (see col. 5, lines 40-52, and

binding fragment thereof (see col. 5, line 60-63, in particular) bind to the extracellular cellular domains of EGFR (see col. 12, lines 7-11, in particular). The reference antibodies that bind to a different epitope on the extracellular domains of EGFR inherently have synergistic effect in blocking or inhibiting the EGFR receptor specific pathway signaling compared with a composition comprising single antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference pharmaceutical composition wherein the induction of receptor dimerization of ErbB receptor molecules of the same specificity (homodimer) or different specificity (heterodimer) with p185neu is enhanced because of the synergistic effect in reducing cancer tumor growth in mice (see col. 3, lines 36-42, in particular). The '157 patent further teaches an immunoconjugate such as antibodies or binding fragment thereof specific for epidermal growth factor receptor is conjugated to or fused to other types of molecule or biologically effective polypeptide or protein such as a cytotoxic molecule, a drug or a radioactive molecule to enhance the tumor reducing properties of the antibodies for treating cancer (see col. 5, lines 53-67 bridging col. 6, lines 1-7, claims 5-6 of the '157 patent, in particular). Thus, the reference teachings anticipate the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No. 4,943,533 (of record, issued July 24, 1990; PTO 892).

The teachings of the '157 patent have been discussed supra.

The invention in claim 11 differs from the teachings of the reference only in that the pharmaceutical composition wherein the second antibody is a murine monoclonal antibody MAb 225 that binds to a different epitope on the ErbB1 receptor (EGFR).

The '533 patent teaches various monoclonal antibodies such as MAb 528, MAb 225, 579 and MAb 455 that bind to the different epitope on the same human epidermal growth factor receptor (ErbB 1) where one antibody competes with the ligand for binding to the receptor and the other antibody binds to the receptor but does not compete with the ligand (see entire document, col. 3, line 46-53, col. 8 through 10, in particular). The reference murine monoclonal antibody 225 inhibits the growth of A-431 tumor cells in the absence of ligand (see col. 8, lines 15, in particular) while the reference murine monoclonal antibody 528 competes with the ligand EGF for binding to the EGFR *in vivo* (see col. 3, lines 46-55, col. 6, lines 39-42, in particular) and inhibits EGF stimulated protein kinase activity (signaling pathway) in A-431 tumor cells (see col. 7, lines 45-54, in particular). The '533 patent teaches that monoclonal antibody 225 binds to a single class of receptor sites on all three cell types by blocking the binding of EGF to EGFR on A-431 cells (see col. 8, lines 59-68, in particular); the C225 antibody inhibits the proliferation of tumor cells in concentration dependent manner (see col. 9, lines 9-10, in particular). The '533 patent teaches monoclonal antibodies that bind to different epitopes on epidermal growth factor receptor may be of considerable therapeutic use and diagnostic uses (see abstract, col. 1, lines 60-68, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art with the expectation of success in combining the EGFR (erbB1) monoclonal antibody MAb 425 or chimeric antibody thereof that binds specific for the extracellular domain epidermal growth factor receptor as taught by the '157 patent with the murine monoclonal antibody such as MAb 225 that binds to a different epitope on the same EGFR as taught by the '533 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because the '533 patent teaches monoclonal antibodies that bind to different

epitopes on epidermal growth factor receptor may be of considerable therapeutic use and diagnostic uses (see abstract, col. 1, lines 60-68, in particular). The '157 patent teaches antibody that binds to EGFR such as monoclonal antibody MAb 425, chimeric antibody thereof or binding fragment thereof that binds to the extracellular domain of human EGF receptor is useful for treating cancer.

In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

15. Claims 1, 10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No 5,558,864 (issued Sept 24, 1996; PTO 892) and Ye et al (Oncogene 18: 731-738, 1999; PTO 892).

The teachings of the '157 patent have been discussed supra.

The invention in claim 12 differs from the teachings of the reference only in that the pharmaceutical composition wherein the first antibody is humanized MAb 425 (h425) instead of murine or chimeric 425 antibody that binds to a first epitope on the ErbB1 receptor (EGFR) and the second antibody is chimeric MAb 225(c225) that binds to a different epitope on the same ErbB1 receptor.

The '864 patent teaches humanized monoclonal antibody such as h 425 that binds to EGF receptor derived from murine monoclonal antibody MAb 425 (see entire document, claims of the '864 patent, in particular). The '864 patent teaches the advantages of humanized antibody h425 is that the humanized is less likely than either mouse 425 antibodies to raise an immune response in humans and more efficacious when used therapeutically in humans than either the mouse or chimeric 425 antibodies since the humanized antibody has a longer half-life in humans and the least likely to arise adverse immune response in human patient with tumor (see col. 22, lines 1-15, in particular).

Ye et al teach C225 is a human-mouse chimeric anti-EGF receptor MAb derived from MAb 225; this chimeric MAb 225 fully retains the activity of murine in competing with EGF for receptor binding and produces a similar or even improved spectrum of anti-tumor activities on a variety of xenograft human cancer (see page 731, col. 2 last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the murine or chimeric 425 antibody that binds to a first epitope on the ErbB1 receptor (EGFR) as taught by the '157 patent for the humanized version of murine monoclonal antibody 425 antibody as taught by the '864 patent and then combine with the chimeric antibody MAb 225 (c225) as taught by Ye et al to form a pharmaceutical comprising a humanized MAb 225 and a chimeric MAb 225 (c225). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because the advantages of humanized antibody 425 are that the humanized antibody is the least likely to arise adverse immune response in human patient as taught by the '864 patent (see col. 22, lines 1-15, in particular) and the humanized antibody h425 has a longer half-life in humans. The '157 patent teaches a pharmaceutical composition comprising multiple antibodies that bind to different epitopes on the extracellular domains of EGFR (a member of Her2 family) has synergistic effect in reducing cancer tumor growth in mice (see col. 3, lines 36-42, in particular). In re Kerkhoven, 205USPQ 1069 (CCPA 1980), recognized that "it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose....[T]he idea of combining them flows logically from their having being individually taught in the prior art" (see MPEP 2144.06).

16. Claims 1 and 13-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No. 5,861,449 (issued Jan 1999; PTO 892).

The teachings of the '157 patent have been discussed supra.

The invention in claim 13 differs from the teachings of the reference only in that the pharmaceutical composition further comprising a cytotoxic agent.

The invention in claim 14 differs from the teachings of the reference only in that the pharmaceutical composition further comprising a chemotherapeutic agent.

The invention in claim 15 differs from the teachings of the reference only in that the pharmaceutical composition further comprising a chemotherapeutic agent wherein the

chemotherapeutic agent is any of the compounds of the group: cisplatin, doxorubicin, gemcitabine, docetaxel, paclitaxel, and bleomycin.

The invention in claim 16 differs from the teachings of the reference only in that the pharmaceutical composition further comprising a cytotoxic agent wherein the cytotoxic agent is an ErbB receptor inhibitor, a VEGF receptor inhibitor, an anti-angiogenic agent or a cytokine.

The invention in claim 17 differs from the teachings of the reference only in that the pharmaceutical composition wherein the first and/or second antibody is an immunoconjugate wherein the antibody portion is fused by its C-terminus to a biological effective protein.

The invention in claim 18 differs from the teachings of the reference only in that the pharmaceutical composition wherein the first and/or second antibody is conjugated or fused to a cytokine at the C-terminus.

The '449 patent teaches a pharmaceutical composition comprising one or more VEGF receptor inhibitor such as DC101 monoclonal antibody, or chimeric antibody thereof that binds to the extracellular domain of VEGF receptor such as Flt-1 (see entire document, col. 8, lines 1-50, col. 7, lines 4-5, in particular) alone or in combination with a cytotoxic agent or chemotherapeutic agent such as cisplatin, doxorubicin, taxol (see col. 7, lines 4-11, in particular) or a cytokine such as CSF (see col. 19, lines 34-35, in particular). The reference pharmaceutical composition comprises the reference antibody and the anti-neoplastic drug or chemotherapeutic drug as separate molecules (see col. 7, lines 9-11, in particular) or a conjugate (see col. 7, lines 11-14, in particular) to provide even more efficient treatment for inhibiting the growth of tumor cells than the use of the antibody by itself (see col. 7, lines 4-9, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine or conjugating the monoclonal Mab 425, or a chimeric antibody thereof that binds to the extracellular domain of human EGF receptor (ErbB1) in the pharmaceutical composition as taught by the '157 patent with the various cytotoxic agent or chemotherapeutic agent such as cisplatin, doxorubicin, taxol, VEGF receptor inhibitor such as DC101 or cytokine such as CSF as taught by the '449 patent for a method of treating cancer. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because the '449 patent teaches the combination of antibodies and anti-neoplastic drug or chemotherapeutic drug as separate molecules or as a conjugate provides even

more efficient treatment by inhibiting the growth of tumor cells than the use of the antibody by itself (see col. 7, lines 4-9, in particular). The '157 patent teaches antibody that binds to EGFR such as monoclonal antibody MAb425, chimeric antibody or binding fragment thereof that binds to the extracellular domain of human EGF receptor is useful for treating cancer. The recitation of antibody portion is fused to the C terminus to a biological effective peptide instead of the N terminus is within the purview of one of skilled in the art to not to block the binding of the antibody or antibody fragment from binding to the extracellular domain of the EGFR (erbB1).

17. Claims 19-23, and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No 6,342,219 (filed April 28, 2000; PTO 892).

The '157 patent teaches a pharmaceutical composition comprising at least one antibodies specific for epidermal growth factor receptor (also known as ErbB1) and at least one antibody that binds to p185c-neu (also known as ErbB2 or HER2 or EGFR2) for treating tumor (see claim 4 of the '157 patent). The term "at least one" implies the reference composition comprising one or more antibodies of the same ErbB1 receptor type. The term "comprising" is open-ended. It expands the claimed pharmaceutical composition to include additional antibodies such as one or more antibodies that bind to p185c-neu as taught by the '157 patent. The '157 patent teaches an antibody that binds to the extracellular domain of human EGFR such as a monoclonal antibody MAb425 and it inhibits EGF binding to its receptor and induces EGF receptor down-regulation without stimulating EGF receptor tyrosine kinase activity (see claim 4 of the '157 patent, col. 12, line 7-11, in particular). The '157 patent teaches another monoclonal antibody that binds to EGFR such as M294 from ICN biomedicals (see col. 7, lines 38-40, in particular). The '157 patent teaches monoclonal antibodies that bind to the extracellular domains may be selected by screening for binding to the extracellular domains of EGFR (see col. 4, lines 64-67 bridging col. 5, lines 1-7, col. 2, lines 37-42, in particular). The reference EGFR extracellular domains to which the reference antibodies bind are located within the EGF ligand binding domains because the reference antibodies such as MAb425, chimeric antibodies (see col. 5, lines 40-52, and binding fragment thereof (see col. 5, line 60-63, in particular) bind to the extracellular cellular domains of EGFR (see col. 12, lines 7-11, in particular). The reference antibodies that bind to a different epitope on the extracellular domains of EGFR inherently have synergistic effect in blocking or inhibiting the EGFR receptor specific pathway signaling compared with a

composition comprising single antibody. Since the Patent Office does not have the facilities for examining and comparing the antibodies of the instant invention to those of the prior art, the burden is on applicant to show that the prior art antibody is different from the claimed antibody. See In re Best. 562 F.2d 1252, 195 USPQ 430(CCPA 1977). The reference pharmaceutical composition wherein the induction of receptor dimerization of ErbB receptor molecules of the same specificity (homodimer) or different specificity (heterodimer) with p185neu is enhanced because of the synergistic effect in reducing cancer tumor growth in mice (see col. 3, lines 36-42, in particular). The '157 patent further teaches an immunoconjugate such as antibodies or binding fragment thereof specific for epidermal growth factor receptor is conjugated to or fused to other types of molecule or biologically effective polypeptide or protein such as a cytotoxic molecule, a drug or a radioactive molecule to enhance the tumor reducing properties of the antibodies for treating cancer (see col. 5, lines 53-67 bridging col. 6, lines 1-7, claims 5-6 of the '157 patent, in particular).

The invention differs from the teachings of the reference only in that a pharmaceutical kit comprising (i) a first package comprising a first antibody molecule, or a portion thereof, which comprises binding sites that bind to a first specific epitope present on a ErbB 1 receptor molecule, and (ii) a second package comprising a second antibody molecule which comprises binding sites that bind to a second different specific epitope on the same ErbB 1 receptor molecule type.

The '219 patent teaches a pharmaceutical kit comprising distinct containers for each desired agent where combined therapeutics are provide (see col. 102, lines 5-31, in particular). The '219 patent teaches such kit contains all the necessary reagents and means for commercial sale for treating cancer (see col. 102, lines 52-63, in particular). The '219 patent further teaches various cytotoxic agents such as ricin A-chain toxin, Pseudomonas toxin (see col. 89, line 24-33, in particular), chemotherapeutic agents such as doxorubicin, cisplatin (see col. 90, line 4-10, col 114, lines 13-27, col. 115-118, in particular), cytokines such as IL-1, and IFNs (see col. 114, lines 1-12, in particular), and VEGF receptor inhibitor such as 2C3 antibody that binds to VEGF (claims of the 195 patent, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to put the first and second antibodies that bind to different epitope on the same ErbB1 receptor (EGFR) as taught by the '157 patent in a kit comprising distinct containers for each desired agent for treating tumor as taught by the '219 patent. One would have been motivated, with a reasonable expectation of success to do this for convenience and commercial

expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '219 patent (See column 102, lines 41-61, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

18. Claim 24 is rejected under 35 U.S.C. 103(a) as being unpatentable over 5,705,157 (of record, issued Jan 6, 1998; PTO 892) in view of US Pat No 6,342,219 (filed April 28, 2000; PTO 892) as applied to claims 19-23 and 25-28 and further in view of US Pat No 5,558,864 (issued Sept 24, 1996; PTO 892) and Ye et al (Oncogene 18: 731-738, 1999; PTO 892).

The combined teachings of the '157 patent and the '219 patent have been discussed supra.

The invention in claim 24 differs from the combined teachings of the references only in that the pharmaceutical kit wherein the first antibody is humanized MAb 425 (h425) instead of murine or chimeric 425 antibody that binds to a first epitope on the ErbB1 receptor (EGFR) and the second antibody is chimeric MAb 225(c225) that binds to a different epitope on the same ErbB1 receptor.

The '864 patent teaches humanized monoclonal antibody such as h 425 that binds to EGF receptor derived from murine monoclonal antibody MAb 425 (see entire document, claims of the '864 patent, in particular). The '864 patent teaches the advantages of humanized antibody h425 is that the humanized is less likely than either mouse 425 antibodies to raise an immune response in humans and more efficacious when used therapeutically in humans than either the mouse or chimeric 425 antibodies since the humanized antibody has a longer half-life in humans and the least likely to arise adverse immune response in human patient with tumor (see col. 22, lines 1-15, in particular).

Ye et al teach C225 is a human-mouse chimeric anti-EGF receptor MAb derived from MAb 225; this chimeric MAb 225 fully retains the activity of murine in competing with EGF for receptor binding and produces a similar or even improved spectrum of anti-tumor activities on a variety of xenograft human cancer (see page 731, col. 2 last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the murine or chimeric 425 antibody that binds to a first epitope on the ErbB1 receptor (EGFR) as taught by the '157 patent in the kit as taught by the '219 patent

for the humanized version of murine monoclonal antibody 425 antibody as taught by the '864 patent and then combine the chimeric antibody MAb 225 (c225) as taught by Ye et al to form a pharmaceutical kit comprising a first container comprising a humanized MAb 225 and a second container comprising a chimeric MAb 225 (c225). From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with the expectation of success to do this because the advantages of humanized antibody 425 are that the humanized antibody is the least likely to arise adverse immune response in human patient as taught by the '864 patent (see col. 22, lines 1-15, in particular) and the humanized antibody h425 has a longer half-life in humans. The '157 patent teaches multiple antibodies that bind to different epitopes on the extracellular domains of EGFR (a member of Her2 family) has synergistic effect in reducing cancer tumor growth (see col. 3, lines 36-42, in particular). Ye et al teach C225 is a human-mouse chimeric anti-EGF receptor MAb derived from MAb 225 and this chimeric MAb 225 fully retains the activity of murine in competing with EGF for receptor binding and produces a similar or even improved spectrum of anti-tumor activities on a variety of xenograft human cancer (see page 731, col. 2 last paragraph, in particular). One would have been motivated, with a reasonable expectation of success to put the various reagents in a kit for convenience and commercial expedience. A kit will allow for ease of use for the practitioner since all the necessary reagents, standard and instructions for use are included in a kit as taught by '219 patent (See column 102, lines 41-61, in particular).

19. No claim is allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

21. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Patent Examiner
Technology Center 1600
May 28, 2007